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Mitral Valve Enlargement in Chronic Aortic Regurgitation as a Compensatory Mechanism to Prevent Functional Mitral Regurgitation in the Dilated Left Ventricle

Jonathan Beaudoin, MD,* Mark D. Handschumacher, BS,* Xin Zeng, MD,* Judy Hung, MD,* Eleanor L. Morris, RDCS,* Robert A. Levine, MD,* Ehud Schwammenthal, MD, PHD†

Boston, Massachusetts; and Tel Hashomer, Israel

Objectives The aim of this study was to test the hypothesis that mitral valve (MV) enlargement occurring in chronic aortic regurgitation (AR) prevents functional mitral regurgitation (FMR).

Background Chronic AR causes left ventricular (LV) dilation, creating the potential for FMR. However, FMR is typically absent during compensated AR despite substantial LV enlargement. Increased mitral leaflet area has been identified in AR, but it is unknown whether increased MV size can represent a compensatory mechanism capable of preventing FMR.

Methods Database review of 816 patients with at least moderate AR evaluated the prevalence of FMR. A total of 90 patients were enrolled prospectively for 3-dimensional echocardiography (30 AR, 30 FMR, and 30 controls) to assess MV geometry including total leaflet area.

Results FMR was present in 5.6% of AR patients by database review. Prospectively, only 1 AR patient had more than mild FMR despite increased LV end-diastolic volume (82 ± 22, 86 ± 23, and 51 ± 12 cm^3/m^2, respectively, for AR, FMR vs. control patients; $p < 0.01$) and similar sphericity index, annular area, and tethering distances compared with FMR. Total MV area was largest in AR (31.3% greater than normal), increasing significantly more than in FMR. The ratio of valve size to closure area was maintained in AR, whereas decreases in this ratio and LV ejection fraction independently predicted FMR.

Conclusions FMR prevalence is low in chronic AR. MV leaflet area is significantly increased compared with control and FMR patients, preserving a normal relationship to the area needed for closure in the dilated LV. Understanding the mechanisms underlying this adaptation could lead to new therapeutic interventions to prevent FMR.
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Functional mitral regurgitation (MR) is a common complication of cardiomyopathies associated with higher mortality (1–4). Its mechanisms have been related to left ventricular (LV) enlargement and distorted shape, restricting mitral valve (MV) closure (5–8). However, LV remodeling alone fails to explain why MR severity varies among individuals with similar degrees of tethering (9). Recent evidence showed that MV leaflets can enlarge in response to LV morphological changes (9–12), with the potential to reduce MR (10). Experimentally, mechanical stretch can promote adaptive MV growth (11), but little is known about the clinical implications of this phenomenon. A naturally occurring setting in which MV adaptation can be studied is in patients with chronic aortic regurgitation (AR), in whom functional MR is infrequent (13,14) despite often severe LV dilation (6,8,13–21). This absence of MR challenges the concept linking functional MR (FMR) solely to LV remodeling. Interestingly, necropsy data previously demonstrated MV enlargement in chronic AR (22), but this finding has

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From the *Cardiac Ultrasound Laboratory, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; and the †Sheba Medical Center, Tel Hashomer, Israel. Dr. Beaudoin is funded by an AHA-Founders Affiliate post-doctoral fellowship grant 10POST4580055. Supported in part by grant 07CVD04 of the Leducq Foundation, Paris, France, for the Leducq Transatlantic MITRAL Network, and by NIH K24 HL67434 and R01 HL109506. Dr. Schwammenthal is a consultant to Medtronic Ventor Technologies Ltd. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Abbreviations and Acronyms

3D = 3-dimensional
AR = aortic regurgitation
FMR = functional mitral regurgitation
LV = left ventricular
MR = mitral regurgitation
MV = mitral valve

not been related to FMR or its determinants in vivo. Whether this phenomenon can be seen as an adaptation counterbalancing LV dilation to prevent MR is unknown.

We tested the hypothesis that MV enlargement occurs in chronic AR and preserves normal mitral geometry relative to the dilated left ventricle to prevent MR. We first assessed FMR prevalence in chronic AR by database review. We then prospectively enrolled patients for 3-dimensional (3D) echocardiography to assess MV size and its relation with LV geometry and function in patients with either chronic AR or MR (ischemic or nonischemic) and in normal control patients using recently developed capabilities for measuring MV area noninvasively (10).

Methods

Retrospective analysis. To assess the prevalence of MR in patients with AR, we searched our institutional echocardiographic database for patients older than 18 years of age with moderate or severe AR who had a transthoracic echocardiogram within the past 5 years. Exclusion criteria were more than mild systolic dysfunction (left ventricular ejection fraction [LVEF] <40%), LV regional wall motion abnormality, severe aortic stenosis (valve area <1.0 cm^2), MV organic pathology (prolapse, rheumatic disease, mitral cleft, endocarditis, and extensive annular calcification), presence of an aortic or mitral prosthesis, and Marfan syndrome. In all patients having more than mild MR, the echocardiographic images were reviewed to confirm the presence of FMR.

Prospective recruitment. From January 2011 to June 2012, we prospectively enrolled 90 subjects for 3D echocardiography: 30 consecutive patients who had at least moderate AR without any previously stated exclusion criteria, 30 patients with moderate or severe FMR (ischemic or nonischemic) and LV end-diastolic dimension comparable to the AR group, and 30 normal control patients (age and sex comparable to AR group) with normal echocardiograms and without known cardiac disease (patients with treated hypertension and no evident LV hypertrophy were not excluded). AR severity was assessed with an integrative approach using color Doppler (vena contracta), regurgitant volume and fraction, and assessment of flow reversal in the descending aorta (23). MR was graded as trace, mild, moderate, or severe integrating color Doppler jet area and vena contracta width (23–25). Medical records were consulted to assess the cause and known duration of AR. All patients gave informed consent before enrollment. The study was approved by the hospital's institutional review board.

Echocardiography. All prospectively enrolled patients underwent standard transthoracic echocardiography using a Philips iE33 scanner with a 5-MHz transducer (Philips Healthcare, Andover, Massachusetts). Full-volume 3D datasets were obtained from the apical window using an X3 matrix-array transducer. The analysis was performed by a single observer using QLAB 5.1 (Philips Healthcare) and custom software for MV area and tethering geometry (Omni 4D, M.D.H.). The 3D datasets were analyzed separately and blinded to the presence and severity of AR and MR. The 3D LV end-diastolic and end-systolic volumes were measured. LV sphericity was evaluated by the ratio of short-axis diameter/long-axis length at end-diastole and end-systole (8,26). Midsystolic (identified by frame count) tethering distances from papillary muscle tips to contralateral annulus (26) were measured from the 3D dataset. Midsystolic mitral annular area was calculated as the projection of the annular trace onto its average or least-squares plane. Total mitral leaflet area was measured in diastole (Fig. 1) using a previously described and validated method that integrates valve area traced from the 3D dataset (10). Closure area was defined as the closed leaflet surface between the LV and left atrium in mid-systole, and thus represents the minimal area that needs to be covered by the leaflets to occlude the mitral orifice. The ratios of total leaflet to annular area and of total leaflet area to closure area were calculated to assess the adequacy of leaflet adaptation relative to LV and annular changes. Dimensions, areas, and volumes were indexed for body surface area. MV thickness was measured in the 2-dimensional echocardiography datasets in the parasternal long-axis view in a diastolic frame without rapid motion with the leaflets as perpendicular as possible to the echocardiographic beam to take advantage of its axial resolution (27–29). As FMR can be related to decreased closing forces in a failing ventricle (30,31), we also measured key parameters of LV contractility including 3D calculated LVEF, end-systolic wall stress reflecting afterload (32,33), and end-systolic volume index, which is relatively preload independent. In the absence of continuous-wave Doppler in the patients without MR to provide true transmitral pressure, mitral closing forces were estimated as: force (N) = 0.0133 · systolic arterial pressure (mm Hg) · leaflet area (cm^2).

Statistics. Continuous variables are expressed as mean ± SD and categorical variables as number (percentage). Differences in proportions were assessed by the chi-square test. Logistic univariate and multivariate regressions were used to assess the predictors of significant MR in the database population. Age, sex, LVEF, and LV end-diastolic and end-systolic dimensions were included in the model. In the prospectively recruited population, echocardiographic variables of the AR group were compared with those of the FMR and control groups. Differences in means among the 3 groups were assessed by 1-way analysis of variance with Bonferroni multiple-comparison tests. We assessed the differential relationship of mitral leaflet area and LV end-diastolic volume by linear regression including group (AR or FMR) as an interaction term. Known AR duration and

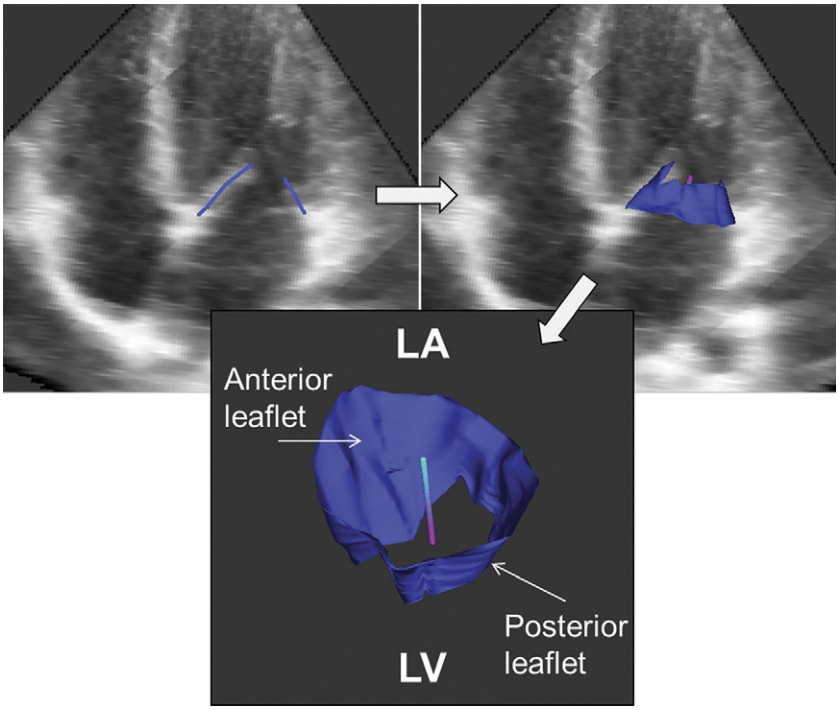

Figure 1 **Mitral Valve Reconstruction for Total Leaflet Area Measurement Using 3-Dimensional Echocardiography**

Sequential leaflet tracing in multiple planes allows computation of total mitral leaflet area (measurable clearly only in diastole because the systolic areas of leaflet coaptation cannot be uniformly visualized [10]). LA = left atrium; LV = left ventricle.

leaflet area in the AR group was also assessed with linear regressions. Leaflet thickness and area were compared among patients with AR jets that were central versus posteriorly directed onto the anterior mitral leaflet. Multivariate logistic regression was used to assess the relationship of total leaflet to closure area ratio and the presence of MR, including in the model variables describing LV function that were significant among FMR and AR patients by univariate analysis: LVEF, end-systolic wall stress, and end-systolic volume index. Regression coefficients standardized for SD were computed. Statistical analysis was performed with Stata/IC 11.2 (StataCorp LP, College Station, Texas).

Results

Retrospective review. We identified a total of 816 patients with moderate or severe AR (Table 1). Moderate or severe FMR was found in 46 patients (5.6%). Age ($p < 0.01$), LVEF ($p < 0.01$), LV end-diastolic ($p < 0.01$), and end-systolic dimensions ($p < 0.01$) were significant predictors of MR. On multivariate analysis, age ($p < 0.01$), sex ($p < 0.01$), and LV end-diastolic dimension ($p = 0.02$) were significant.

Prospective study. A total of 90 patients were enrolled (30 patients with AR, 30 patients with FMR, and 30 normal control patients); their characteristics are shown in Table 2. Causes of AR were endocarditis (5 patients, with infection resolved medically), congenital aortic valve disease (n = 21), and aortic root dilation (n = 4), and the median known AR duration was 24 months (range, 1 month to 10 years). The AR and control groups were not significantly different in age, sex, body surface area, or comorbidities (hypertension and diabetes); more of the AR patients were treated with renin-angiotensin system blockers for afterload reduction compared with control patients (57% vs. 27%, $p = 0.04$). Only 1 patient in the AR group had more than mild (moderate to severe) MR, with LV enlargement, mild global dysfunction, and incomplete mitral leaflet closure. FMR patients were similar in sex, but older than control patients and AR patients. The FMR group mostly consisted

Table 1 **Echocardiographic Characteristics of Moderate to Severe Aortic Regurgitation Patients**

	Total Population (N = 816)	MR (n = 46)	No MR (n = 770)	p Value
Age, yrs	64 ± 18	72 ± 14	63 ± 18	<0.01
Males	499 (61)	22 (48)	477 (62)	0.06
LVEF, %	64 ± 9	61 ± 11	65 ± 8	<0.01
LVIDed, mm	49 ± 8	52 ± 8	49 ± 8	<0.01
LVIDes, mm	32 ± 7	36 ± 8	32 ± 7	<0.01

Values are mean ± SD or n (%).

LVEF = left ventricular ejection fraction; LVIDed = left ventricular internal diameter at end-diastole; LVIDes = left ventricular internal diameter at end-systole; MR = mitral regurgitation.

Table 2 Echocardiographic Characteristics of Aortic Regurgitation, Functional Mitral Regurgitation, and Control Patients

Characteristics	AR (n = 30)	Normal (n = 30)	FMR (n = 30)	p Value
Age, yrs	47 ± 17*	45 ± 17	69 ± 14†	<0.01
Males	22 (73)	15 (50)	18 (60)	0.20
Body surface area, m^2	1.9 ± 0.2	1.8 ± 0.2	1.9 ± 0.2	0.06
MR more than mild	1 (3)	0 (0)	30 (100)	<0.01
LVEDV, cm^3	154 ± 46†	92 ± 23	167 ± 52†	<0.01
LVEDV index, cm^3/m^2	82 ± 22†	51 ± 12	86 ± 23†	<0.01
LVESV, cm^3	62 ± 25*†	33 ± 12	106 ± 44†	<0.01
LVESV index, cm^3/m^2	33 ± 13*†	18 ± 7	55 ± 20†	<0.01
LVEF, %	61 ± 7*	64 ± 7	37 ± 11†	<0.01
Diastolic sphericity ratio, D/L	0.52 ± 0.07†	0.44 ± 0.05	0.52 ± 0.05†	<0.01
Systolic sphericity ratio, D/L	0.44 ± 0.06†	0.36 ± 0.07	0.47 ± 0.06†	<0.01
Midsystolic tethering distance, medial PM, mm	43 ± 7†	38 ± 4	41 ± 6	<0.01
Midsystolic tethering distance, lateral PM, mm	42 ± 7†	36 ± 5	39 ± 5	<0.01
Leaflet area, cm^2	16.8 ± 3.7†	12.8 ± 2.3	15.4 ± 2.7†	<0.01
Leaflet area index, cm^2/m^2	8.9 ± 1.6*†	7.1 ± 1.3	8.0 ± 1.4	<0.01
Midsystolic closure area, cm^2	12.1 ± 2.8†	9.7 ± 1.9	12.6 ± 2.0†	<0.01
Midsystolic annulus area, cm^2	9.9 ± 2.2†	8.2 ± 1.6	10.0 ± 1.5†	<0.01
Leaflet area/closure area ratio	1.4 ± 0.2*	1.4 ± 0.2	1.2 ± 0.1†	<0.01
Leaflet area/annulus area ratio	1.7 ± 0.2*	1.6 ± 0.2	1.5 ± 0.2	<0.01
End-systolic wall stress, $\times 10^3$ dyn/cm^2	83 ± 23*	71 ± 23	135 ± 48†	<0.01
Closing force, N	28.0 ± 8.6†	20.3 ± 3.9	25.3 ± 6.1†	<0.01

Values are mean ± SD or n (%). *p < 0.05 versus FMR group. †p < 0.05 versus control group.
AR = aortic regurgitation; D = left ventricular short-axis diameter; FMR = functional mitral regurgitation; L = left ventricular long-axis dimension; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; PM = papillary muscle.

of patients with ischemic cardiomyopathy (25 ischemic, 5 nonischemic), and none of these patients had more than mild AR.

AR and FMR patients had a comparable increase in LV volumes compared with control patients (end-diastolic volume index: 82 ± 22 vs. 86 ± 23 vs. 51 ± 12 cm^3/m^2 for the AR, FMR, and control groups; $p < 0.01$). Also, LV sphericity index, tethering distances, annulus area, and closure area were all similarly increased in the AR and FMR groups compared with control patients. End-systolic wall stress was significantly increased in FMR compared with AR and control patients, consistent with increased afterload, and comparable to the results of Reichek et al. (32). Mitral closing force was increased in both FMR and AR groups compared with control patients, driven by increased leaflet and annular area. The 3D MV closure area, annulus area, and total leaflet area are shown in Table 2 and Figure 2. Total mitral leaflet area was the largest in AR patients (31.3% larger than normal, 16.8 ± 3.7 cm^2 vs. 12.8 ± 2.3 cm^2 for controls, $p < 0.01$), with comparable differences persisting when normalized to body surface area. There was a significant relationship between valve size and AR regurgitant volume ($p = 0.01$). Although FMR patients also had some degree of valve enlargement, the magnitude was significantly less than in AR patients (Table 2). The ratio of total leaflet area to systolic closure area was preserved in the AR group and identical to that of control patients (1.4 ± 0.2 in both groups, $p = 0.26$), indicating adequate leaflet compensation for the increased area requirements demanded by the dilated LV. In contrast, this ratio was significantly decreased in FMR patients (1.2 ± 0.1, $p < 0.01$ vs. control and AR groups), indicating a relatively

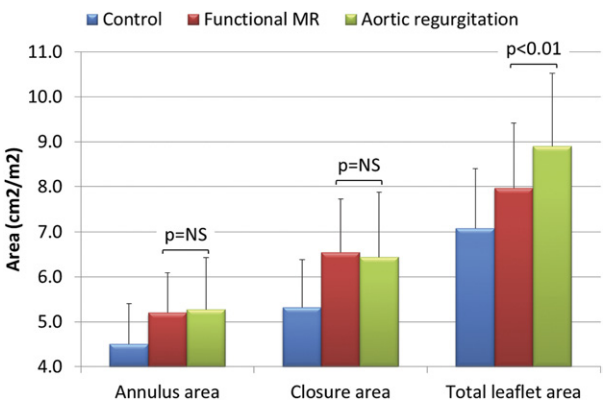

Figure 2 Total Leaflet Area, Midsystolic Closure, and Annulus Areas in Control, Functional Mitral Regurgitation, and Aortic Regurgitation Patients

The midsystolic closure and annulus areas are both similarly increased in aortic regurgitation (AR) and functional mitral regurgitation (MR) patients compared with control patients. In AR, there is a proportional increase in total valve area, maintaining a normal relationship between valve and left ventricular sizes (manifested by a normal ratio of total leaflet area to closure area), which is not the case in patients with functional MR.

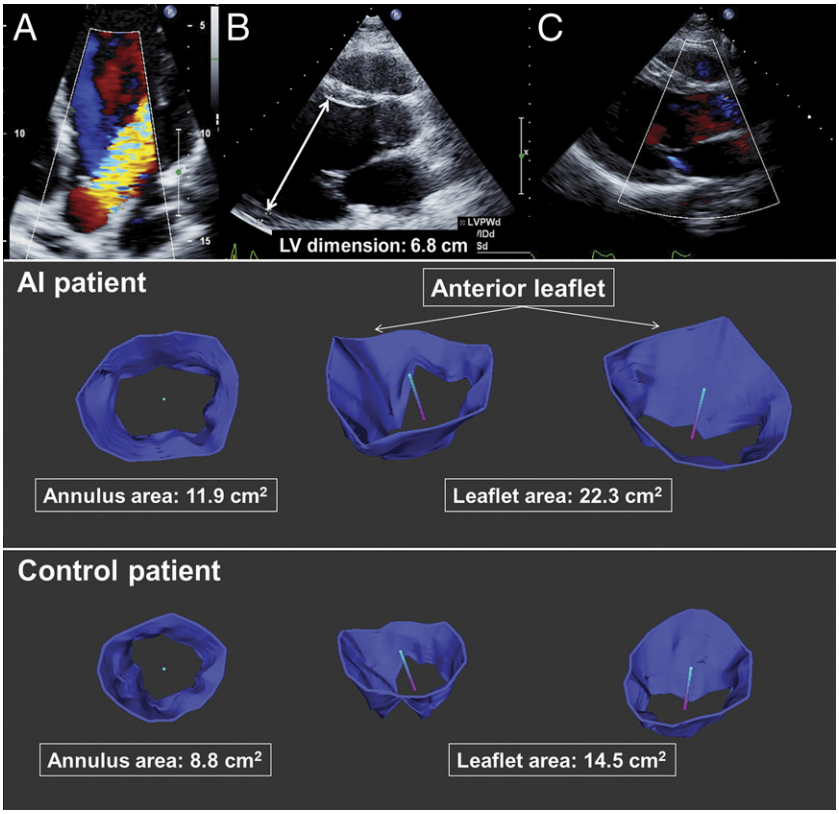

Figure 3 **Example of Mitral Valve Enlargement in Aortic Regurgitation**

Representative example showing 3-dimensional reconstructions of control and chronic aortic regurgitation patients. **Top row:** Transthoracic echocardiogram showing severe aortic regurgitation **(A)**, a dilated left ventricle at 6.8 cm **(B)**, and only trace mitral regurgitation **(C)**. **Middle row:** Different projections of a 3-dimensional reconstruction of the mitral leaflets showing increased annulus size and larger leaflet area. **Bottom row:** Same reconstruction in a control patient matched for age and body surface area. LV = left ventricular.

smaller valve in relation to the dilated LV and annulus. There was no significant relationship between age and leaflet to closure area ratio in any studied group or the overall population ($p = 0.20$). The ratio of total leaflet area to annulus area showed the same pattern (1.7 ± 0.2 vs. 1.5 ± 0.2 vs. 1.6 ± 0.2 for AR, FMR, and controls; $p < 0.01$ between AR and FMR) with a preserved ratio in AR patients and a reduced one in FMR patients. Patients with AR and FMR also had increased mitral leaflet thickness compared with controls (2.4 ± 0.3 mm vs. 2.5 ± 0.6 mm vs. 2.1 ± 0.4 mm for AR, FMR, and control patients; $p < 0.01$). An example of increased 3D leaflet area in a patient with severe AR and a dilated left ventricle but only trace MR versus a control patient with comparable age and body surface area is shown in Figure 3.

In both the AR and FMR groups, there was a significant linear relationship between MV leaflet area and LV end-diastolic volume. However, the magnitude of valve enlargement relative to LV size was greater in AR patients (Fig. 4) ($p = 0.004$ between FMR and AR groups). Twenty-one of the 30 AR patients had the regurgitant jet posteriorly directed onto the anterior mitral leaflet, but without any difference in mitral leaflet area or thickness compared with those with central jets (leaflet area, 8.8 cm^2/m^2 vs. 9.0 cm^2/m^2; $p = 0.86$; anterior thickness, 2.5 ± 0.3 mm vs. 2.4 ± 0.5 mm; $p = 0.76$). There was no effect of known AR time duration on the degree of MV enlargement ($p = 0.45$). A subset of 5 patients had a history of aortic valve endocarditis and sudden onset of moderate to severe AR. These patients were not significantly different from other AR patients with regard to LV volume and MV leaflet area in the chronic compensated state studied by 3D echocardiography.

Multivariate predictors of MR. Table 2 presents a univariate comparison of means between the AR, FMR, and control groups. LVEF, end-systolic wall stress, and end-systolic volume index were significantly different in the AR group compared with the FMR group, and these differences could affect MR severity. In a multivariate analysis controlling for those variables, the ratio of total leaflet/closure area remained significantly associated with the presence of MR (standardized regression coefficient of 0.07, $p = 0.029$) along with LVEF (standardized regression coefficient of 0.04, $p = 0.025$); end-systolic volume index and end-systolic wall stress had p values of 0.057 and 0.098, respectively.

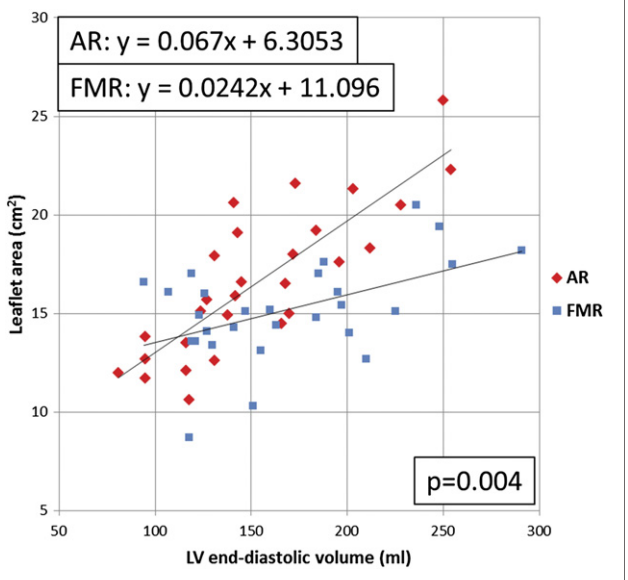

Figure 4 **Relationship Between Total Leaflet Area and Left Ventricular Volume in Aortic Regurgitation and Patients With Functional Mitral Regurgitation**

In both groups, there is a linear relationship between mitral valve size and left ventricular (LV) volume. The increase in valve size is, however, greater in patients with aortic regurgitation (AR) compared with those with functional mitral regurgitation (FMR). MR = mitral regurgitation.

Discussion

The results of this study show that despite an enlarged left ventricle, increased sphericity, longer tethering distance, and a dilated mitral annulus, patients with chronic compensated AR have a surprisingly low incidence of FMR. Although the absence of MR is consistent with the usually slow clinical evolution of chronic compensated AR, this observation challenges the current concepts relating FMR solely to LV remodeling. A 3D reconstruction of the MV valve showed that AR patients have a compensatory increase >30% in their mitral leaflet area, which remains proportional to the LV volume and the demands it imposes in terms of mitral systolic closure area. Interestingly, the AR group also had slightly thicker mitral leaflets, suggesting that enlargement is not due to passive stretch alone and raising the possibility of active growth of cells, matrix, or both. In contrast, patients with FMR had a proportionally smaller valve increase despite similar LV size, sphericity index, and tethering distances, suggesting possible factors that can limit or favor MV growth depending on the underlying pathophysiology. The ratio of total leaflet area to the area required for leaflet closure, a strong determinant of MR (10), was also preserved in AR and reduced in FMR. Valve area increased more steeply with increasing LV end-diastolic volume in AR versus FMR. These results are in accordance with the necropsy data of Mautner et al. (22) that showed increased MV area and mass in AR, and add to the observations of relatively lesser increases in MV area in FMR, with a decreased ratio of total to closure leaflet areas. Of note, the absolute valve areas obtained in our study are greater than those reported by necropsy, which may relate to different measurement methods. In the necropsy study, the leaflets were formalin fixed and excised 2 to 3 mm caudal to the annulus, which, when spread over the entire annulus, can make a substantial difference in total area. The relative increase in area compared with the control group was similar in both studies.

These results add to the growing literature suggesting that valve leaflets are able to remodel and adapt in response to LV morphological changes rather than being only passive flaps. Interestingly, increased aortic leaflet dimensions have also been reported in patients with AR and aortic root dilation, suggesting aortic valve adaptation (34). Insights from recent animal studies suggest that MV mechanical stretch can induce valve growth (11) by reactivating embryonic development pathways, also shown with mechanical stretch of in vitro valve constructs (35). Of note, the same in vivo study showed significant valve enlargement after only 60 days of mechanical stretch. This is consistent with our subset of patients having shorter AR evolution but the same degree of valve enlargement in the chronic state of LV dilation. Although mechanical stretch is likely involved, other potential mechanisms may also stimulate valve growth. It has been shown that LV eccentric hypertrophy in AR is the result of numerous extracellular matrix genes being modulated in the myocardium (36), and expression of these genes is also modified in MR-induced volume overload (37). It is possible that MV tissue shares some of these molecular remodeling mechanisms present in the LV myocardium, which could promote valve enlargement in parallel with LV dilation. Interestingly, a previous animal study of LV pressure overload was associated with not only MV but also tricuspid valve changes, leading the authors to suggest the possibility of circulating factors inducing valve remodeling (38).

Implication for FMR. We demonstrate here that the compensated chronic AR population shows adequate mitral leaflet adaptation, even with severe LV dilation. In addition to disturbed ventricular geometry, FMR is the result of an imbalance between closing and tethering forces (30,31). Importantly, a larger valve and annulus not only provide more tissue to cover the increased closure area, but also contribute to greater closing forces (proportional to area). In the multivariate analysis, the leaflet-to-closure area ratio was a strong predictor of FMR, independent of LVEF, systolic wall stress, and LV end-systolic volume index. Decreased LVEF, which reflects the underlying cardiac pathology but also the additional remodeling imposed by the presence of MR, was also significant. The presence of MR therefore depends on both leaflet enlargement and LV contractility. This adaptation is, however, inadequate in patients with FMR (less valve enlargement despite comparable LV size), which remains common in ischemic and myopathic heart failure. It will therefore be relevant in future work to

consider factors that can potentially impair leaflet growth in these patients. Interestingly, although valve enlargement can promote mitral coaptation, other results have suggested that leaflet remodeling can potentially induce maladaptive valve stiffness and fibrosis, interfering with valve function (39–41). This suggests that mitral leaflet remodeling could be a double-edged sword, preventing MR in certain situations, but with the potential to contribute to MR in other cases. One major difference between our chronic stable AR population and other ischemic or nonischemic cardiomyopathies is the preserved systolic function and the absence of clinical heart failure. Heart failure is associated with strong humoral and proinflammatory cytokine activation, factors well known to induce and modify remodeling in the LV and numerous other organs. Although renin-angiotensin and adrenergic systems are also activated in chronic AR (42,43), the magnitude of this activation in asymptomatic patients with preserved function is likely lower than what is seen in the setting of ischemic and nonischemic systolic dysfunction. It is currently unknown whether this exaggerated humoral activation can modify valve leaflet growth, although the profibrotic effects of angiotensin are well described (44,45). Future mechanistic studies are warranted to explore the factors potentially limiting leaflet growth and flexible closure because they could eventually represent future therapeutic targets.

Study limitations. The observed increases in leaflet area and thickness suggest possible cellular growth activation, but no biological samples were available in this imaging study. Our study shows that compensated AR is associated with adequate MV adaptation, but the biological mechanisms leading to valve growth need to be explored. We are currently planning additional studies looking at valve area over time in chronic AR, acute AR, and the transition to decompensated heart failure, in which clinical experience indicates that FMR is more common. Also, the influence of other variables such as age, medication, and comorbidities on MV adaptation and incidence of FMR in various populations (ischemic and nonischemic heart failure) needs to be assessed in clinical studies designed to address those influences.

Conclusions

Patients with chronic, clinically stable moderate to severe AR have a large increase in mitral leaflet size. This increase is proportional to the LV enlargement and, in addition to preserved contractility, can represent an adaptive mechanism to prevent FMR in a dilated ventricle. Further mechanistic studies are needed to explore how we can modulate this adaptation to prevent FMR in other diseases.

Reprint requests and correspondence: Dr. Ehud Schwammenthal, Heart Center and Cardiac Rehabilitation Institute, Sheba Medical Center, Tel Hashomer 52621, Israel. E-mail: ehudsc@gmail.com.

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